

Parasagittal High-Convexity Tightness Reveals a Focal Site of CSF Outflow Impairment in Ventriculomegaly

Afroditi Despoina Lalou

afroditi.lalou@umu.se

Umeå University

Sara Qvarlander

Umeå University

Sofia Behndig

Umeå University

Jan Zizka

Umeå University

Jan Malm

University Hospital of Umeå

Anders Eklund

Umeå University

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Abstract

Introduction

Disproportionately enlarged subarachnoid space hydrocephalus (DESH) and resistance to CSF outflow (R_{out}) are two of the most consistent diagnostic and prognostic markers in normal pressure hydrocephalus, yet it remains unclear whether they reflect a common pathophysiological process. A plausible link is that tightness of the high convexities adjacent to the superior sagittal sinus (SSS), the principal CSF outflow region, compromises CSF drainage and thereby increases R_{out} . To test this hypothesis, we investigated the association between parasagittal high-convexity CSF volume near the SSS and R_{out} in subjects undergoing MRI and CSF infusion testing.

Methods

We conducted a retrospective study of 621 individuals (581 with ventriculomegaly and 40 without), investigated with CSF infusion testing and brain MRI. Parasagittal high convexity CSF volumes were quantified using a semi-automated segmentation approach, focusing on anatomically defined high convexity regions. R_{out} was derived from lumbar CSF infusion testing using standardised protocols. Associations between parasagittal CSF volume and R_{out} were evaluated using correlation analyses, with additional assessment of demographic and structural confounders.

Results

An inverse relationship was observed between parasagittal high convexity CSF volume and R_{out} ($N = 621$, Spearman $Rho = -0.42$, $p < 0.001$). This association was most pronounced when measurements were restricted to anatomically localised regions adjacent to the SSS, while more extended convexity regions demonstrated weaker relationships ($N = 309$, $Rho = -0.14$, $p = 0.0002$). The observed association was preserved after exclusion of healthy individuals. Age, sex, and ventricular volume did not significantly influence the relationship.

Conclusions

A localised relationship exists between parasagittal high-convexity morphology and resistance to CSF outflow. The regional specificity of this association suggests that DESH and R_{out} may reflect a shared pathophysiological mechanism, which becomes apparent only when examined at anatomically strategic sites along the CSF outflow pathway.

Introduction

Ventriculomegaly is frequently encountered in the elderly and associated with normal pressure hydrocephalus (NPH), one of the few potentially treatable causes of cognitive and gait impairment in older adults(1–5). Symptomatic improvement after CSF drainage and shunting(5), is closely linked to

CSF hydrodynamics, particularly resistance to CSF outflow (R_{out})(6–11). In parallel, disproportionately enlarged subarachnoid space hydrocephalus (DESH), characterised by enlarged Sylvian fissures and sulcal effacement at the high convexities (tight high-convexity subarachnoid spaces), is one of the most widely used imaging markers in the clinical assessment of NPH(12–16). While advanced MRI techniques have improved our ability to distinguish between the potentially reversible NPH and irreversible atrophy (e.g. from Alzheimer's, Parkinson's and Parkinsonism)(12,17–19), a critical gap remains in understanding how morphological features relate to CSF dynamics -the key pathophysiological target of shunt treatment.

The parasagittal high-convexity region is of particular interest because it lies adjacent to the superior sagittal sinus (SSS), a critical hub for CSF drainage via pressure gradients through arachnoid granulations, and meningeal lymphatic vessels(20–26). One potential consequence of ventriculomegaly is cerebral uplift, whereby ventricular enlargement displaces the brain upward and reduces the superior subarachnoid spaces(27). As a result, both high-convexity tightness and elevated R_{out} may represent manifestations of the same mechanical deformation, reflecting a common pathophysiological process rather than independent findings. Such compression of the CSF outflow pathway by the parenchyma itself remains largely uninvestigated. Altered CSF outflow physiology could equally contribute to the emergence or persistence of this morphology. The anatomical proximity of high-convexity tightness to the SSS nevertheless makes this region a plausible site for a morphology-physiology relationship.

Despite their importance in the diagnosis and outcome prediction of NPH, it remains unknown how R_{out} and DESH are related and whether they reflect a shared pathophysiological mechanism. Hence, the aim of this study was to investigate the association between R_{out} and high convexity tightness adjacent to the SSS in subjects evaluated with CSF infusion test as well as brain MRI.

Methods

Patients and healthy individuals

The Hydrocephalus Unit at Umeå University Hospital is a tertiary referral center specialising in the assessment and treatment of hydrocephalus and CSF dynamic disorders. A standardized diagnostic workup is routinely employed, and between 2007 and 2019, 671 patients underwent both lumbar infusion testing and brain MRI. As the primary aim was to investigate the association between resistance to CSF outflow and high-convexity sulcal effacement irrespective of diagnosis, all eligible patients were analyzed as a single cohort.

Diagnoses included idiopathic and secondary NPH, congenital hydrocephalus (either arrested or decompensated), as well as differential diagnoses (ventriculomegaly with another dementia disorder).

From the 671 subjects who had undergone both a complete preoperative infusion test and a 3D T1-weighted MRI scan, we excluded 3 with poor quality MRI, and 87 with unreliable R_{out} values or

incomplete infusion test. This resulted in a cohort of 581 patients, The age range of the entire cohort was 57–84 years, median 74 years, with 375 men and 246 women.

In addition, 40 healthy individuals 60–82 years were included to ensure that normal physiological and anatomical variation was adequately represented in the analyses. The group has been described in detail in previous publications (28,29).

In our analysis, we deliberately included all subjects and avoided diagnostic subgrouping, as such stratification would reduce statistical power, introduce selection bias, and shift the focus from the physiological mechanism under investigation to diagnosis-specific comparisons.

Ethical considerations

Ethical approval was obtained from the Swedish Ethical Review Authority (Registration No. 2020–04469). The study was conducted in accordance with the Declaration of Helsinki. Given the retrospective study design, patients who were alive at the time of study inclusion were informed about the study by letter and provided with the opportunity to opt out of participation.

Resistance to CSF outflow

The infusion tests were performed according to standardised local protocols, typically with constant-pressure infusion. Whenever the constant-pressure technique had failed, the protocol was reverted to constant-rate infusion. The technique and data analysis are described in detail in several publications, including the comparison between the different infusion methods (28,30–32).

In brief, two needles are inserted in the lumbar intrathecal space, one for infusion and one for CSF pressure monitoring. A servo-controlled CSF dynamics apparatus (Celda, Likvor AB) automatically initiates and terminates the process under the supervision of an experienced nurse. The patient lies in the supine position and the external auditory meatus is used as the zero reference point. After a baseline recording of 15–20 minutes, the pressure is increased in steps at 4–6 predetermined levels or one longer-duration level (constant-pressure), or increased through infusion at 1.5ml/min for a maximum of 30 minutes, or until CSF pressure surpasses the safety threshold (constant infusion). CSF pressure was recorded with 100Hz sampling frequency and was, for this study, post-processed in MATLAB.

Two separate raters visually inspected all pressure-flow curves and calculation output to remove artefacts that could influence the R_{out} estimation and exclude cases with insufficient data quality (ADL and SQ). In case of doubt or discrepancy, we decided on exclusion or artefact removal after consensus discussion with a senior third rater (AE). We calculated R_{out} as the difference between the plateau and baseline CSF pressure divided by the infusion rate of Ringer's lactate, as described previously(33). The healthy individuals' R_{out} values were taken from the previous publication as reported(28).

Image acquisition

3D T1-weighted spoiled gradient echo sequences had been acquired with 1.5 or 3T MR scanners between 2007 and 2019 with slight variations in acquisition protocols and image resolution across the study period. All images were aligned to the anterior-posterior commissure line, mid-sagittal plane, and bias corrected using the Python library SimpleITK before proceeding to extract CSF volumes.

Segmentation of CSF spaces

To assess the high convexity CSF volumes, we used the programme imlook4d (<https://janaxelsson.github.io/imlook4d/>) and a script made for selecting the parasagittal volumes of interest developed and described by Behndig et al. (<https://github.com/SofiaBehndig/qDESH>).

In short, the tool identifies and extracts the relevant CSF volumes through a two-step process: first, defining specific search volumes in the high convexities, and lateral ventricles, and then segmenting CSF within these volumes using a threshold based on difference in signal intensity between CSF and gray matter.

The high-convexity search volumes were manually delineated along the bicommissural line. The primary region of interest extended from the posterior commissure to 2 cm anteriorly and is hereafter referred to as the **parasagittal volume (PSV)** (Fig. 1). An additional extended region of interest, spanning 3 cm anterior and 3 cm posterior to the posterior commissure, was defined to sample a larger portion of the parasagittal outflow region (Fig. 2). This region is referred to as the **extended parasagittal volume (ePSV)**.

The rationale for the extended ROI was to include a broader segment of the SSS region, encompassing a larger spatial distribution of arachnoid granulations and thereby providing a more comprehensive assessment of parasagittal CSF outflow anatomy. Both ROIs initially contained combined brain and CSF tissue but excluded the SSS itself. The superior boundary was therefore defined by the dura and the inferior wall of the SSS. The script subsequently identified the interhemispheric fissure and restricted the search regions to 3 cm in width (1.5 cm on either side of the midline) and 1 cm in height below the dura and SSS. Details of the segmentation are shown in the figures (Fig. 1b-d, Fig. 2a&b).

Besides the search volumes at the high convexities, we selected a search volume at the lateral ventricles, which was inflated enough pixels to infiltrate the surrounding grey matter (Fig. 1c-d). From this volume, we detected the threshold for the CSF segmentation (ref Behndig et al) and then extracted the volume of the lateral ventricles for each individual. The same threshold was also applied to extract the two high convexity CSF volumes of interest.

Inter-rater variability

The inter-rater variability of the original segmentation method has been previously validated and reported in Behndig et al as excellent (0.99 Intraclass coefficient with 0.988–0.995 95% confidence interval, $p < 0.001$). We validated the 6-cm long high convexity CSF volume for the purpose of this article and it was 0.97 ICC, with 95% CI of 0.951–0.985.

Statistics

Statistical calculations were performed with R version 4.4.1.

The threshold for statistical significance was set at p-values below 0.01.

Spearman correlation coefficient (ρ) was used to assess the relationship between the high convexity volumes and R_{out} . This non-parametric method assesses monotonic relationships based on ranked data and was preferred over Pearson's correlation because the observed relationships were non-linear and inconsistent with parametric assumptions of linearity and normality.

To further evaluate the association while accounting for potential confounders, we fitted a generalised linear model with the inverse of R_{out} ($1/R_{out}$) as the dependent variable and parasagittal high convexity volume, baseline CSF pressure, age, sex, and lateral ventricular volume as independent variables.

Finally, we performed a post-hoc of the healthy individuals separately, as well as after removing them from the cohort, in order to assess whether the relationship depended strongly on the variance that their values provided.

Results

Resistance to CSF outflow and High Convexity Volumes

There was a correlation between the PSV and R_{out} with $\rho = -0.42$, $p < 0.001$, $N = 621$. The correlation (non-parametric, Spearman test) is illustrated in (Fig. 3).

For the healthy group, the correlation between R_{out} and PSV was $\rho = -0.25$, $p = 0.1225$, $N = 40$. Without the 40 healthy individuals, the relationship for the patient group was: $\rho = -0.43$, $p < 0.001$, $N = 581$.

The 6-cm long parasagittal CSF volume was assessed in 309 individuals in total and resulted in $\rho = -0.14$, $p = 0.0002$, $N = 309$). The relationship for the 2-cm long parasagittal CSF volume in the corresponding group was $\rho = -0.43$, $p < 0.001$, $N = 309$. The correlation is illustrated in Fig. 4.

Covariance and interactions

Relationship with Age and Sex

Neither age nor sex correlated with high convexity volumes or R_{out} , nor influenced the relationship of the 2-cm parasagittal CSF volume with R_{out} .

Lateral Ventricular Volume and baseline CSF Pressure

For all 621 individuals, there was no correlation between the PSV and lateral ventricular volumes ($Rho = -0.08$, $p = 0.074$). There was a significant, though weak inverse relationship between the PSV and baseline CSF pressure ($R = -0.18$, $p < 0.001$). R_{out} positively correlated with baseline CSF pressure ($Rho = 0.20$, $p < 0.001$) and with the lateral ventricular volume ($Rho = 0.16$, $p < 0.001$).

For the healthy, the corresponding relationships were: $Rho = -0.05$, $p = 0.74$ (parasagittal CSF volume - baseline CSF pressure), $Rho = 0.31$, $p = 0.057$ (R_{out} - baseline CSF pressure), and $Rho = 0.065$, $p = 0.69$ (R_{out} - lateral ventricular volume).

In our generalised linear model, baseline CSF pressure ($\beta = -0.0025$, $p = 0.00055$) and lateral ventricular volume ($\beta = -0.00012$, $p = 0.0027$) contributed to the relationship between $1/R_{out}$ and the PSV.

Adding interaction terms to the model did not produce any significant result and the association between the 2cm-long parasagittal CSF volume and $1/R_{out}$ was not modified.

Discussion

In this study, we combined MRI-based volumetric analysis with CSF infusion measurements and identified a localised association between parasagittal high-convexity morphology and resistance to CSF outflow, linking two of the most widely used morphological and physiological markers in hydrocephalus treatment selection and prognostication, namely DESH-like radiological features and R_{out} . The association was strongest in the anatomically focused parasagittal region adjacent to the superior sagittal sinus, suggesting that this area may represent a strategically important interface between morphology and CSF outflow physiology. More broadly, our findings support the concept that ventriculomegaly, cerebral uplift, narrowing of the high-convexity subarachnoid spaces, and impaired CSF outflow may represent interconnected manifestations of a common mechanical process.

The cohort comprised a heterogeneous spectrum of diagnoses, predominantly idiopathic NPH, but also patients with secondary and congenital forms of NPH, as well as with other neurodegenerative disorders (e.g. Parkinson's, parkinsonism, Alzheimer's). In addition, a group of healthy older adults was included as controls. As our aim was to investigate a putative physiological mechanism of CSF outflow impairment, rather than a diagnosis or prognosis-specific phenomenon, all available subjects with ventriculomegaly were analysed together in order to capture the widest possible range of morphologies and R_{out} values. We have avoided subgroup analysis, as it is not relevant to the question we set to ask and will inadvertently lead to between-group comparisons that are not relevant to our aim.

Although the observed relationship was moderate ($Rho = -0.42$), this should be interpreted in the context of the complexity of CSF circulation and outflow. The finding is particularly noteworthy considering the substantial heterogeneity of the cohort and the multifactorial nature of CSF clearance. Rather than detracting from the results, the unexplained variability likely reflects additional anatomical and physiological contributors to outflow resistance. In patients with both parasagittal tightness and elevated R_{out} , the findings thus support the presence of a localised outflow disturbance near the SSS. Conversely, elevated R_{out} in the absence of parasagittal tightness suggests that resistance may arise from alternative anatomical sites that can contribute to R_{out} , including the posterior fossa, foramen magnum, or spinal canal, or from functional impairment of CSF clearance pathways such as the glymphatic and meningeal lymphatic systems described by Ringstad, Eide, Wåhlin and colleagues(21,34,35). Taken together, these observations highlight the importance of identifying anatomically strategic loci when studying CSF dynamics and suggest that focused regional analyses, as shown here for our selected PSV, may reveal pathophysiological mechanisms that are obscured by broader morphological assessments. Importantly, this type of analysis is pertinent, given that the reabsorption pathways of CSF have recently come into question(20,36–40). Our results support that the classical route through the sagittal sinus(41–46) remains relevant for CSF outflow.

Another potential explanation for the variability in the PSV- R_{out} relationship is the heterogeneous anatomy of the SSS. This region contains arachnoid granulations, pressure-dependent drainage routes, and meningeal lymphatic structures; thus, morphological crowding in this area could plausibly hinder CSF passage(47–49). Additionally, heterogeneity across subjects likely reflects individual variation in the number, size, and distribution of arachnoid granulations, as well as differences in skull curvature and the direction of parenchymal displacement. Because arachnoid granulations are broadly distributed and vary in size(47,49–59), tightness measured in the 2-cm-long vertex region would be expected to account for a limited proportion of the R_{out} variability. Even though the majority of arachnoid granulations can be found at the level of the vertex, giant arachnoid granulations can often be found posteriorly, as well as at the transverse sinuses(51,54,57,60–62). Nevertheless, the observation that the 2-cm-long region captured the outflow relationship better than the extended 6-cm-long version could also signify a greater contribution of local anatomical features at the vertex, rather than the overall distribution of arachnoid granulations along the sinus.

Regarding the choice of search volume around the SSS, it was designed to contain only the information relevant to obstruction of CSF pathways in that area. Depending on the condition of the dura and arachnoid (and the presence of convexity blocks), CSF pockets may form across the midline, introducing anatomical variability that is difficult to resolve with current MRI sequences(26,63–68). To minimise the influence of these effects, we deliberately restricted our analysis to the topmost, 1-cm in height, parasagittal region. This approach provides a dual advantage: i) it reduces volume contamination from focal CSF pockets and local geometric irregularities, and ii) it focuses on the anatomically most relevant outflow interface adjacent to the SSS, where the majority of arachnoid granulations are located -primarily in the anterior and superior portions. As such, the measured CSF volume is more likely to reflect the

functional outflow pathway rather than adjacent, anatomically variable spaces. Advanced imaging and physiological measurements may further improve characterisation of these structures.

Neither age nor sex showed a measurable association with R_{out} or with high convexity CSF volumes. However, our age range was 57–84 years(69–72). In contrast, lateral ventricular volume showed a weak but significant association with R_{out} ($R = 0.16$), indicating that ventricular enlargement alone is only weakly related to outflow resistance. Other factors and patterns of ventricular expansion likely contribute but were beyond the scope of this study. These finding show that looking at global CSF dynamic changes and targeted anatomical areas of interest allows for a more comprehensive review that does not only reflect the influence of ageing. The absence of sex-related differences further supports the notion that the secondary mechanical consequences of ventricular enlargement, rather than inherent brain or skull anatomical differences, drive the observed variability in high-convexity morphology and R_{out} .

A potential sequence of pathophysiological events is becoming clearer. Rather than representing a collection of disconnected signs, ventricular enlargement, cerebral uplift, reduction of the high-convexity subarachnoid spaces, and impaired CSF outflow may form part of the same mechanical process. For years, MRI and infusion studies have shown individual features of this process, including DESH, tight or enlarged sulci, and raised or even “normal” R_{out} . Our study places some of these observations within a common pathophysiological framework. Similar analyses should be undertaken at other strategically selected anatomical sites that may provide pathophysiological explanations and/or correlations with neurological signs.

Clinically, the coexistence of high-convexity tightness and elevated R_{out} may reflect a downstream mechanical process potentially amenable to shunting(26,73–82). Several reports have shown that DESH features often improve after CSF diversion(63,83). Shunt treatment reduces the resistance of the CSF drainage system, yet some patients improve despite relatively low preoperative R_{out} values and even without significant high-convexity tightness. The relationship between these morphological and physiological changes therefore remains incompletely understood. Unfortunately, it cannot be explored post shunting as postoperative CSF infusion test will predominantly measure the fixed resistance of the shunt and not the native CSF outflow pathways.

Limitations

Measurement uncertainty in R_{out} remains an inherent challenge of the lumbar infusion test, where small leaks, or variations in spinal canal compliance can influence the pressure–flow relationship and introduce noise into the final estimate. Although we applied strict quality control and excluded artefactual recordings, these physiological and technical factors may still contribute to variability in R_{out} independent of cranial CSF outflow. Finally, while our segmentation method reduces the influence of focal enlarged sulci, subtle anatomical variations may still affect volumetric precision. These limitations

highlight the need for complementary physiological and imaging approaches to further refine our understanding of CSF outflow impairment in ventriculomegaly.

Conclusions

By combining MRI-based volumetry with CSF dynamics, we show that tightness immediately adjacent to the superior sagittal sinus is associated with higher R_{out} , whereas broader convexity measures, ventriculomegaly and demographic factors are not. These findings highlight the importance of parasagittal subarachnoid space effacement as a potential mediator of CSF outflow impairment and underscore the value of anatomically targeted imaging markers for understanding the complex pathophysiology of CSF circulation in ventriculomegaly.

Declarations

Competing Interests

S.Q. has received honoraria by Likvor AB for lecturing and educational material. The authors report no other competing interests.

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Author Contribution

A.D.L. and A.E. conceived and designed the study. A.D.L. performed the data analysis, interpreted the results, prepared the figures, and wrote the main manuscript text. S.Q. contributed to study design, data collection, curation and interpretation, and manuscript revision. S.B. developed and validated the MRI volumetric methodology and contributed to data interpretation and manuscript revision. Also contributed to data curation. J.Z. contributed to neuroradiological aspects of the study and manuscript revision. J.M. contributed to study design, clinical interpretation of the findings, and manuscript revision. A.E. conceived the study (together with ADL, as above), supervised the project, contributed to data interpretation, and manuscript revision. All authors reviewed and approved the final manuscript.

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past two decades. This work represents the culmination of a long-standing collaborative effort involving many individuals, whose dedication has enabled the creation of this resource and the scientific insights reported here.

Data Availability

The neuroimaging and infusion test data that the findings of this study composite are kept as per the local and national policies from Umeå University and Umeå University Hospital. Patient confidentiality and relevant restrictions apply to the availability of these data, which are not publicly available. The data could, however, be made available upon reasonable request, and after approval of the authors.

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Figures

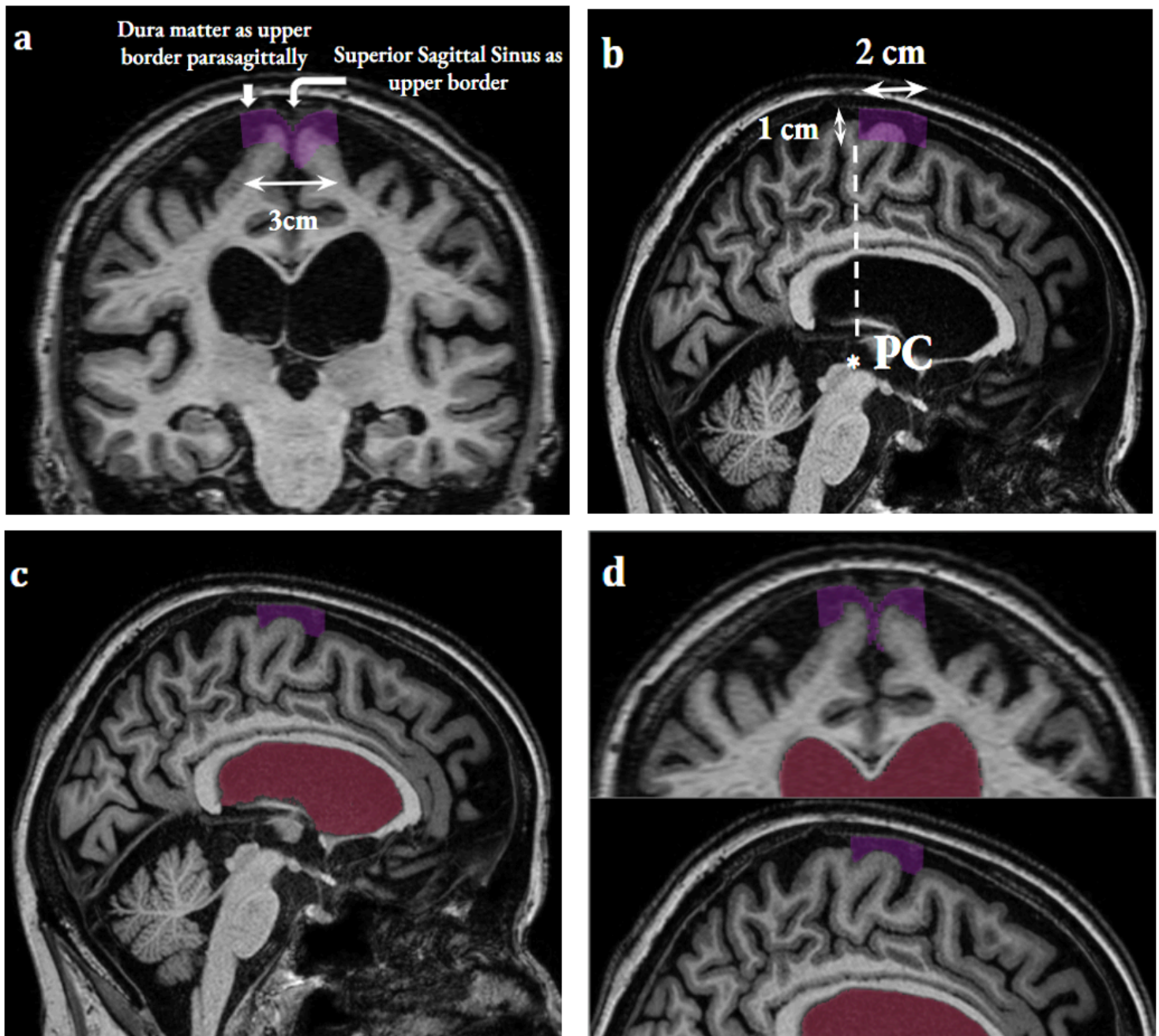


Figure 1

Parasagittal High Convexity Volume, short version, 2cm-long search area anterior the Posterior Commissure. a. Coronal view of the search area in the midline, 1.5 cm each side from the

interhemispheric fissure (3cm total). The area closest to the sagittal sinus was selected with a height of 1cm from the dura and the superior sagittal sinus. B. Sagittal view of the search area: 2cm-long search area anterior to the posterior commissure (PC, marked with asterisk) volume. C. Resulting segmentation of the parasagittal high convexity CSF volume in purple. The CSF in the lateral ventricles is shown in magenta. d. Closer view of the segmented CSF volume, coronally and sagittally.

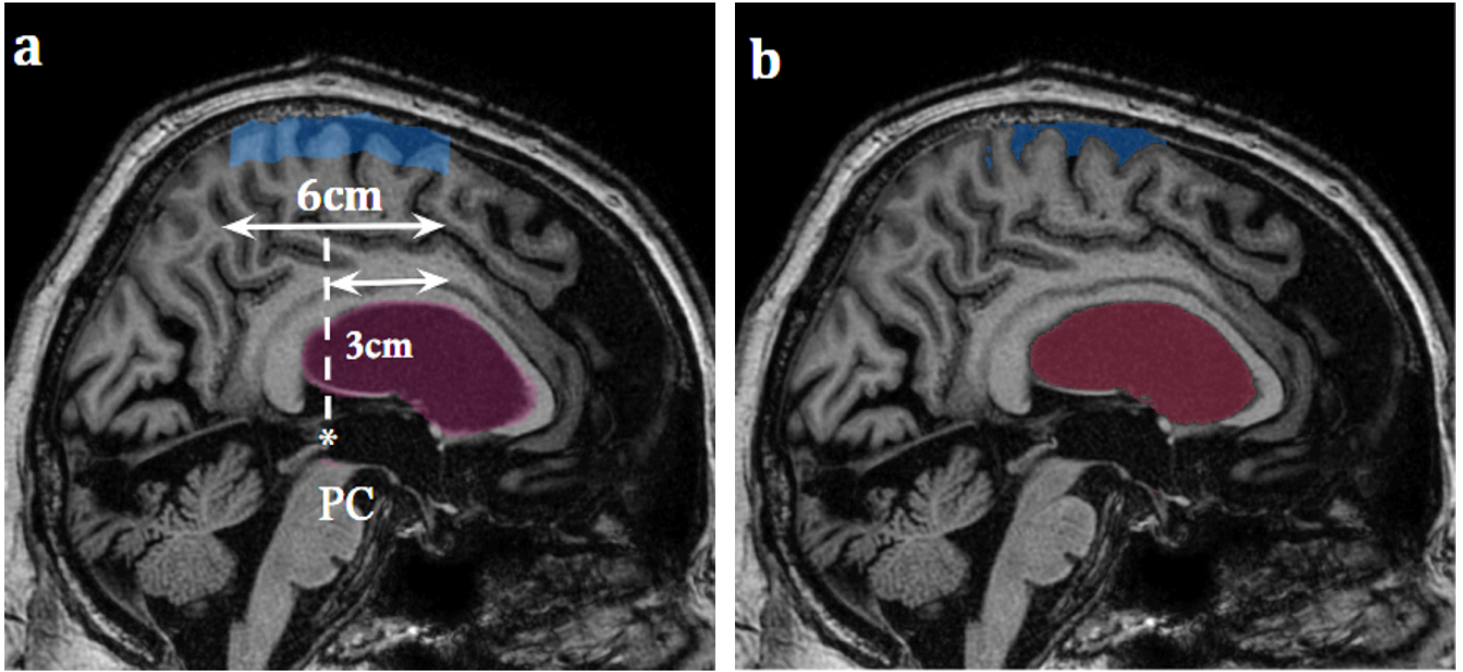


Figure 2

Extended, 6-cm long version of the Parasagittal High Convexity Search Volume, 6cm-long antero-posteriorly to the posterior commissure. a. Similar to Figure 2a&b in height and width, a search area was drawn of total 6cm length, 3cm anteriorly & posteriorly from the posterior commissure (PC, marked with an asterisk). b. The resulting segmented parasagittal high convexity CSF volume after thresholding. As in figure 2, the ventricular CSF volume is shown in magenta.

N = 621, Spearman Rho = -0.42, p <0.0001

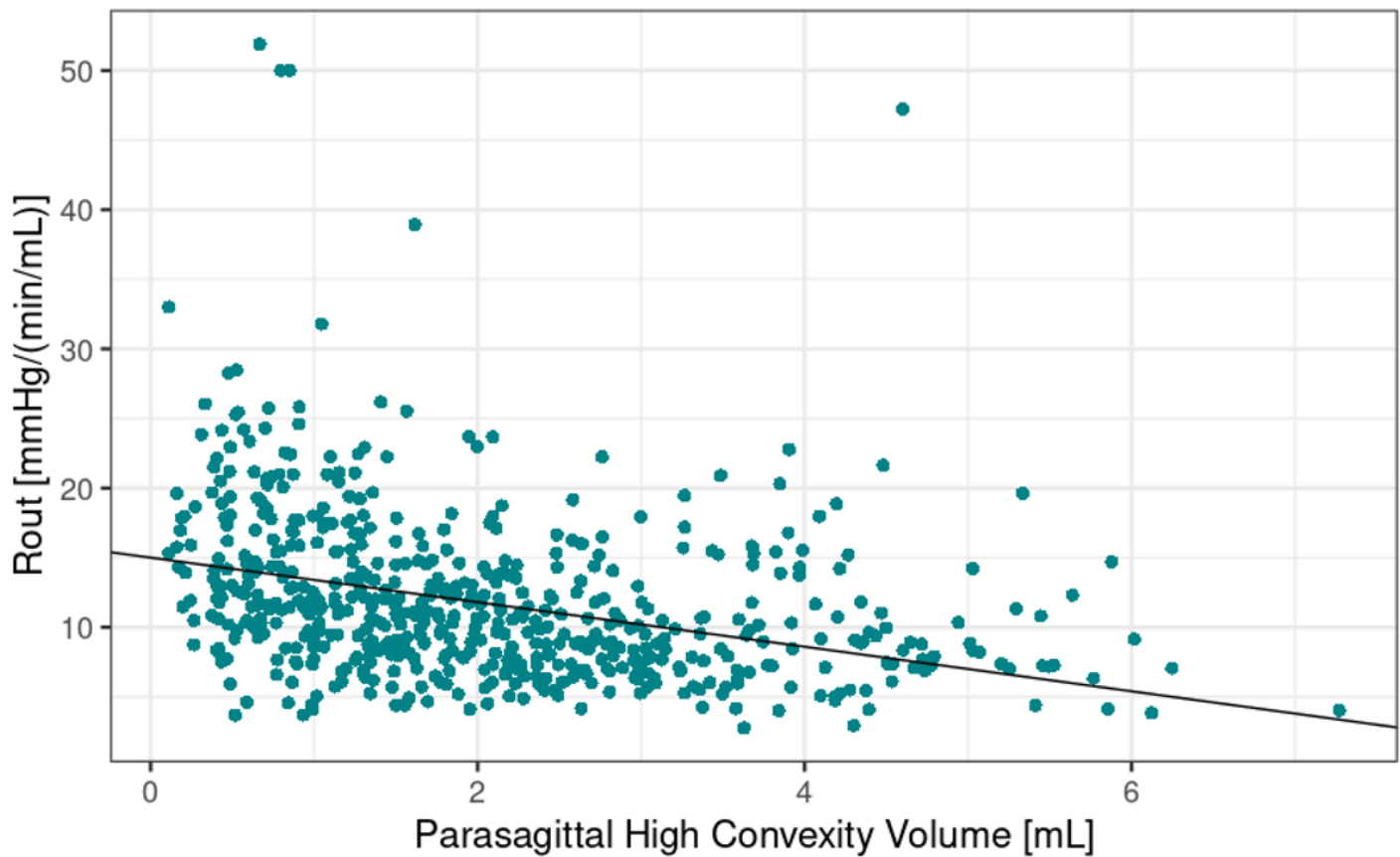


Figure 3

Relationship between the Resistance to CSF outflow (R_{out}) and the 2-cm long Parasagittal High Convexity CSF volume in 621 individuals. *Spearman Rho = Spearman Correlation coefficient. The fitted line is used from the linear model for illustrative purposes only.*

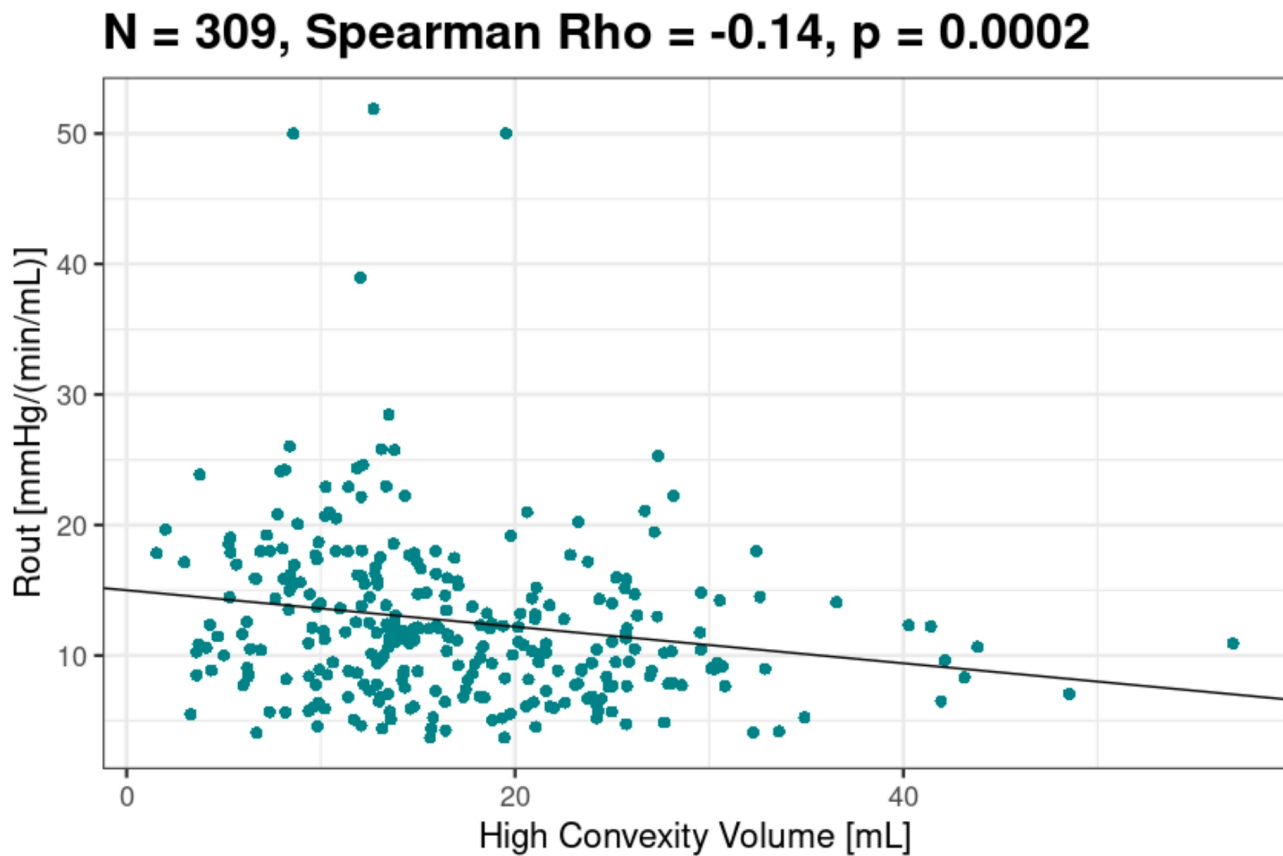


Figure 4

Correlation between the Resistance to CSF outflow and 6-cm Parasagittal High Convexity CSF Volume in 309 individuals with ventriculomegaly. *Spearman Rho = Spearman Correlation coefficient. The fitted line is used from the linear model for illustrative purposes only.*